

REMARKS

The Official Action dated December 27, 2005 and references cited therein have been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Status of the prosecution:

Claims 1, 2, 4-14 and 16-23 are pending. The rejection of claims 1, 2, 4-14 and 16-23 under 35 U.S.C. §112, second paragraph, made in the June 8, 2005 Official Action has been withdrawn in view of the amendments made in Applicants' reply mailed October 6, 2005.

The rejection of claims 1, 2, 4-14 and 16-23 under 35 U.S.C. §103(a), as allegedly unpatentable over Mack et al. in view of Kong et al. as evidenced by McLaughlin et al., made in the June 8, 2005 Official Action has been withdrawn in view of the amendments made in Applicants' reply mailed October 6, 2005.

Claims 1, 2, 4-14 and 16-23 stand newly rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Mack et al. in view of Legerski (U.S. Patent No. 6,406,891, filed September 28, 1998, issued June 18, 2002).

Status of the claims:

The claims have not been amended herein. Applicants submit that the currently pending claims are in condition for allowance, as they are directed to novel and nonobvious subject matter. Support for Applicants' position is set forth below.

The claimed subject matter is not obvious over the teachings of the cited art:

Claims 1, 2, 4-14 and 16-23 stand rejected under 35 U.S.C. §103(a) as unpatentable over the teachings of Mack et al. (Mack) in view of the teachings of Legerski. Applicants traverse this rejection.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been motivated to modify a prior art reference or to combine reference teachings to

arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from Applicants' disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). For the reasons discussed below, a proper *prima facie* case of obviousness has not been set forth.

The Examiner alleges that all of the steps claimed by the instant claims are disclosed by Mack, excepting that the polymerase used for the second strand cDNA synthesis is an *E. coli* DNA polymerase. The Examiner states that the currently claimed method is distinguished from the teachings of Mack because it employs conditions suitable for a Bst large fragment DNA polymerase rather than an *E. coli* DNA polymerase in the second strand synthesis. The Examiner then alleges that Legerski improves the method of generating double stranded cDNAs, "wherein the artisan specifically recognizes the problem associated with generating a second strand cDNA synthesis from a first strand cDNA, that is, the formation of secondary structure." The Examiner goes on to state that "Legerski specifically overcomes this problem by use of a thermostable DNA polymerase *in the second strand cDNA synthesis step*, specifically contemplating Bst DNA polymerase large fragment, allowing for the synthesis of long cDNA molecules" (emphasis added).

Applicants respectfully disagree with the Examiner's characterization of Legerski's teachings. Legerski does not teach *any* change to the second strand cDNA synthesis step. Rather, Legerski is concerned with problems associated with producing long cDNAs, i.e., in the range of more than 5-6 kb (Legerski, Col. 6, lines 2-4). Legerski specifically teaches that the problem is caused by "the occurrence of secondary structures in the mRNA" (Legerski, Col., 6, lines 4-5) as opposed to any feature of the first strand of cDNA after it is formed. Legerski goes on to teach: "[T]hese secondary structures inhibit the progression of the reverse transcriptases and thus prevent the synthesis of full-length *first strand cDNA*" (Legerski, Col., 6, lines 5-8, emphasis added).

Indeed, Legerski teaches the following method, focused on first strand cDNA synthesis, as follows (Legerski, Col. 6, lines 9-16, emphasis added):

As described more completely below, the present invention provides a method of producing full length *first strand* synthesis of cDNA. More particularly, the invention describes a method in which cycling back and forth between a processive RT and a thermostable RT enzyme *during first strand synthesis* allows for the complete production of the *first strand* of a full length cDNA. This invention exploits the notion that the mRNA secondary structures may be removed by elevating the temperature of the RT reaction. It is possible to carry out an RT reaction at the elevated temperatures using a thermostable RT enzymes, however, although these enzymes are operative at high temperatures (55-90°) the reaction is very slow. This inefficiency can be circumvented by adding fresh processive RT enzyme once the impediment of the secondary structure has been bypassed. Thus, the synthesis of the *first strand* can be continued at the lower temperature. This cycling allows the alternate synthesis of the long chain at the lower temperature and removal of the secondary structures at the higher temperature.

It is clear that Legerski's focus is on improving the process of making full length cDNA from long mRNA by temperature cycling in first strand synthesis to remove mRNA secondary structure during that step. Though, as pointed out by the Examiner, Legerski teaches that Bst DNA polymerase large fragment can be used in second strand synthesis, Bst1 DNA polymerase is offered among a laundry list of DNA polymerases, some of which are thermostable and some of which are not (see Legerski, Col. 11, line 48 through Col. 15, line 67). The Examiner fails to point to any motivation for selectively choosing Bst1 DNA polymerase from the various DNA polymerases disclosed in the prior art. Indeed, Legerski does not even recommend Bst DNA polymerase for thermal cycling in first strand synthesis, and even goes so far as to note that "Bst DNA polymerase cannot be used for thermal cycle sequencing" (Legerski, Col. 12, lines 11-12). Thus, Legerski nowhere teaches or suggests that second strand synthesis should or could be carried out at elevated temperature, or in the presence of thermostable RNase H, as is recited in the instant claims.

It can be seen from the foregoing that neither of the cited references provides any hint or suggestion that would have motivated the ordinarily skilled artisan to combine their teachings to arrive at the claimed methods. The prior art fails to teach or suggest a method where *second strand* synthesis is carried out at an elevated temperature of from 45 to 80 °C using the Bst large fragment DNA polymerase and a thermostable RNase H. Nor does the prior art teach or suggest advantages flowing from the claimed methods, such as the ability to

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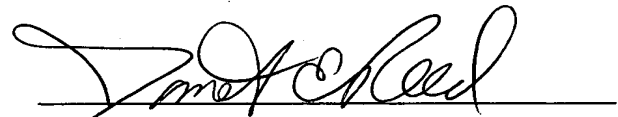
generate relatively large amounts of RNA from a small starting number of cells with high efficiency and in a substantially reduced time period compared to known methods for performing RNA amplification. Any combination in the absence of a "specific hint or suggestion in a particular reference" is thus necessarily the result of impermissible hindsight and is not a proper basis for a *prima facie* of obviousness. *In re Sang Su Lee*, 277 F.3d 1338 (Fed. Cir. 2002). Accordingly, Applicants respectfully assert that a *prima facie* case of obviousness on the basis of the cited references has not been established. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) is therefore requested.

Conclusion:

In view of the foregoing remarks, the presently-pending claims are believed to be in condition for allowance. Applicants respectfully request early and favorable reconsideration and withdrawal of the rejections set forth in the December 27, 2005 Action, and allowance of this application.

Respectfully submitted,

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